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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/117,071	09/25/1998	ALAN JOHN KINGSMAN	9192.5USWO	3270

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	24

DATE MAILED: 12/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/117,071	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-56,58-61 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *47-56, 58-61 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/17/02 has been entered.

Claims 47, 51, 55, 59, 60 and 61 were amended.
Claims 47-56, 58-61 and 63 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF* ***ALL*** *PENDING CLAIMS IS REQUESTED.*

Claim Objections

Applicant is advised that should claim 63 be found allowable, claim 51 will be objected under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The instant claim recites limitation "wherein said producer cell is a fresh cell from a subject" which does not further limit the subject matter as claimed in base claim 51.

Claim 47 is objected to because of the following informalities: The instant claim fails to recite any active steps, which are required to exercise the method as claimed. The part (i) of instant claim should be written in active tense. Changing "conversion" to – converting – is suggested. The parts (ii) and (iii) are not steps performed by practitioner but are the consequences of the only recited process step of part (i). For example "production of replication defective retroviral vector" is the result of a process and not an active step required to exercise the invention as claimed. Appropriate correction is required.

Claim 48 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim recites limitation "the cell isolated from the subject converted into a producer cell ex vivo" which does not further limit the subject matter of base claim 47. The base claim 47 only reads upon a method that requires introduction of a heterologous gene in vivo, since parts (ii) and (iii) are not being done by practitioner but are the [illegible] DNA [illegible] Therefore, claim limitation that requires any ex vivo modification does not further limit the invention as claimed in base claim 47, which lacks any

step for delivery of a cell. It is suggested that claim 48 should be written as an independent claim.

Claim Rejections - 35 USC § 112

Claims 47-56, 58-61 and 63 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of packaging a set of DNA sequences (pHIT456, PHIT111 and pHT60) capable of producing a defective retrovirus particle containing a heterologous gene of interest into a producer cell in vitro, does not reasonably provide enablement for inducing any and all cells into a producer cells into a producer cell ex-vivo or in-vivo such that expression of any and all heterologous gene by said replication defective retrovirus is produced in side a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 01/19/01.

The applicant argues that although the claims may encompass gene therapy, they do not recite gene therapy and do not requires any therapeutic effect (response, page 4, para.2). The applicant argues that the experimentation required to exercise the invention as claimed is not undue, since one skill in the art would be able to introduce a heterologous gene of interest into a target cell considering the instant disclosure (response, page 4, para.3-4).

However, this is not found persuasive because applicant's argument alone cannot take [illegible] Slaughterhouse, 182 USPQ (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re

Fisher, 166 USPQ 19 24 (CCPA 1970)). The only disclosed utility of the invention as claimed is gene therapy (spec. page 1; page 5, lines 20-24). The instant specification fails to disclose any other use for the instant invention. In addition no evidence of another well established utility has been provided. Therefore the applicant's assertion that instant claims do not requires any therapeutic effect based upon a gene-based delivery is considered moot. The invention as claimed clearly recites the use of instant invention in "medicine" wherein the heterologous gene comprises "therapeutic active gene" (see claim 56 and 60). Therefore the invention as claimed clearly falls in the realm of gene therapy.

The courts have clearly stated that a specification need not to disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement*". Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

As evidenced from the earlier office action the gene therapy is considered highly [illegible] and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be

attributed to gene therapy (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Therefore there is need for a greater understanding of an underlying mechanism that contribute to a particular disease. Considering the scope of therapeutic gene (as claimed), it is unclear whether the disease would be the result of the loss of gene product or is the result of altered gene product function. It is even unclear whether the treatment of the disease associated with the gene as claimed would require increase or decrease in the expression of the gene product.

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, in vitro gene transfer studies are not predictive of in vivo gene therapy [illegible] higher in vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides

the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefore would be diluted out before reaching their targets

The gene based therapies or delivery of heterologous gene of interest using a producer cell in in-vivo are not routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claims 51, 52-56, 58 60, 61 and 63 stand rejected under 35 U.S.C. 112, second paragraph being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 51 and 63 recites the term "fresh". It is unclear what is fresh in this context. The applicant argues that the specification defines term "fresh" on page 5, line 36 and extending to page 6 line 6. However, this is not found persuasive because fresh is relative term and considering the definition provided in the instant specification a cell line that has not been [illegible]. Therefore it is unclear what is considered fresh in this context.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 51, 60 and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by Verma et al (US 6013516, filed 10/06/1995). The cited art teaches three plasmid based replication defective retroviral producer system. The first construct comprises a DNA sequence lacking functional env and gag-pol genes and a heterologous gene (transfer vector), the second construct comprises gag and pol genes (packaging construct) and the third construct comprises env gene (env plasmid), see figure 1, col.2, lines 44-67. The cited art further teaches the production of replication defective retroviral particles by transfecting the three plasmid constructs in human kidney producer cells (col.12 example-4, fig-3). The cited art further teaches that heterologous gene comprises a biological response modifier (col.8, line 1-13). Therefore the cited art clearly anticipated the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner